THE RELATION OF PORTAL VENOUS BLOOD FLOW
TO EXPERIMENTAL PORTAL HYPERTENSION

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by

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B.A. Univ. Minnesota 1955

A thesis submitted to the Faculty
of the Yale University School of Medicine
in candidacy for the Degree of Doctor of Medicine

Department of Surgery
Yale University School of Medicine
1959

ACKNOWLEDGMENTS

Dr. William W. L. Glenn, Department of Surgery, who suggested and directed this study.

Dr. Milton Hales, Department of Pathology, and Dr. William Tisdale, Department of Medicine, for their generous advice and criticism.

Mr. Armand Negri, Department of Surgery, who taught the author the value and care of the experimental animal.

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INTRODUCTION

The predominant clinical complication of hypertension of the portal venous system in man is hemorrhage from esophago-gastric varices. Current surgical management of this life-threatening problem is predicated upon the proposition that the clinical and pathologic manifestations of portal hypertension are a direct consequence of elevated portal venous pressures.[1] The fundamental pathologic lesion which has received the greatest attention and which is of most significance in the majority of instances is a mechanical block somewhere within the portal vascular bed. It is presumed that this factor of obstruction results in an increased vascular resistance and a consequent rise in portal pressure with the development of a collateral circulation to effectively by-pass the site of obstruction.

Vascular pressure is, however, a function of volume flow as well as resistance, so that, theoretically, alterations in flow might also lead to changes in portal pressure. The importance of this mechanism would become of practical significance if instances of portal hypertension in the absence of evident obstructive factors could be demonstrated and if abnormally increased blood flows were found within the portal vascular inflow in such instances.

Understanding of the fundamental etiologic and pathogenetic factors in the development of portal hypertension has been handicapped by the inability to reproduce the disease in the experimental animal. It is the purpose of this paper to review the traditional

concepts of the pathogenesis of portal hypertension, emphasizing certain discrepancies which demand a reappraisal of these concepts. A new method will be described for the experimental study of this disease with particular reference to the problem of increased portal venous flow as an etiologic factor in the development of increased portal pressure.

THE PATHOGENESIS OF PORTAL HYPERTENSION

It has been customary to consider portal hypertension as being directly related to intrahepatic or extrahepatic portal venous obstruction, and this has served as a convenient form of classification.[2] The intrahepatic lesions include the various forms of cirrhosis, hemochromatosis, schistosomiasis and hepatic syphilis. There have been numerous studies attempting to correlate the pathological findings, particularly in the cirrhotic liver, with the concomitant existence of portal hypertension. The preparation of corrosion casts of cirrhotic livers injected with gelatin, for example, has demonstrated a marked diminution to the total vascular bed.[3,4] Johnston[5] directly measured the circumference of comparable portal venules and their accompanying hepatic arterioles in normal and cirrhotic livers and observed a significant narrowing of the venules of the latter. In addition to the factor of vascular obstruction in cirrhosis Herrick[6] and later Dock[7] indirectly demonstrated that there were free communications between the hepatic artery and the portal vein; these authors suggested that these arterio-venous communications may be a significant factor in the elevated portal pressures. Injection studies have also demonstrated the presence of arterio-venous shunts as well as communications between the portal and hepatic veins within the liver.[8] Direct observation of arterio-venous anastomoses in the normal rat liver by a technique of direct illumination has revealed that about 75 percent of the hepatic circulation is ordinarily inactive.[9] It is suggested by these observations, therefore, that the elevated portal pressures in cirrhosis are the result of an increased vascular resis-

tance subsequent to a diminished vascular bed as well as increased flow through hepatic arterial-portal venous anastomoses. The relative contribution of these two factors in the genesis of portal hypertension is unknown.

Extrahepatic portal venous obstruction is commonly associated with portal hypertension. Chronic thrombosis of the portal or splenic vein may be caused by neonatal omphalitis[10], pylephlebitis, trauma, thrombocytosis, or neoplastic invasion or pressure.[11] Stenosis of the portal or splenic vein may be the result of congenital malformation,[12,13,14] post-operative adhesions, or tumor compression. Cavernomatous transformation of the portal vein is occasionally the only pathological finding in a case of portal hypertension; it has been postulated that this lesion may represent a recanalized portal vein thrombosis, an hemangioma of the portal vein or a congenital malformation.[15] All of these lesions may become clinically manifest following hemorrhage from esophageal varices, progressive splenomegaly or mild ascites. They are more commonly observed in children[16] and young adults, and characteristically these patients have livers which are functionally and histologically normal. Thrombosis or endophlebitis of the hepatic veins, prolonged and severe congestive heart failure or chronic constrictive pericarditis may also give rise to lesser degrees of elevated portal tensions and splenomegaly.

Although the majority of patients with portal hypertension will be found to have either an intrahepatic or extrahepatic portal venous obstruction, there remains an irreducible minimum of patients in whom no obstructive element can be demonstrated either at autopsy,

operation or by radiologic visualization of the portal system. Among 55 cases of "Banti's Syndrome" observed by Rousselot, no obstructive factor could be found in 22.[17] In a report of 15 cases of assumed extrahepatic portal hypertension with normal liver function and structure this same author was unable to demonstrate the presence of the extrahepatic lesion in seven.[18] With the advent of splenoportography, however, by means of which the entire portal system could be adequately visualized a more sensitive method of determining the presence or absence of vascular obstruction became available.

In Rousselot's papers frequent reference is made to the concept of "Banti's Disease" and "Banti's Syndrome". In a discussion of the pathogenesis of portal hypertension it is pertinent to introduce a discussion of these eponymic entities, even though the theories of Banti have served more to obscure our understanding of the disease than to clarify it.

In 1883 Banti described a disease which he felt was a new and distinct clinical syndrome.[19,20] Essentially, Banti postulated that <u>some</u> cases of portal hypertension were caused primarily by a splenogenous toxin which was a direct cause of the splenic and hepatic pathology observed in his cases. He outlined three phases of this process. The first phase consisted of gradually increasing splenomegaly with anemia and leukopenia; this phase was said to last three to five years or as long as twelve years. The second phase, lasting 12 to 18 months, was characterized by diminishing urine volume with urobilinuria along with painless enlargement of the liver without jaundice or ascites. The final phase was manifested by a shrinking liver, ascites, hepatic insufficiency, jaundice, splenomegaly, gastrointestinal hemorrhage and

death. Banti felt that this sequence of events was initiated and perpetuated by a toxin produced by the spleen. Splenomegaly was a prominent feature of the disease, the spleen seldom weighing less than 1000 grams and often as much as 3000 grams. He described a lesion in the spleen which he felt to be a specific sign of the disease. This lesion consisted of a thickening of the splenic reticulum about the terminal penicillar arterioles with extension into the malpighian corpuscles and their eventual replacement along with periarterial hemorrhage and fibrosis, producing a lesion which was termed "fibroadenie" or siderotic nodule. The subsequent changes in the liver were those of cirrhosis with an associated portal and splenic endophlebitis. The essential feature of this concept was that the changes in the spleen preceded those in the liver, and that the changes in the latter were directly caused by the pathology in the former.

It was quickly demonstrated, however, that many of Banti's cases were caused by other well-known causes of hepatic cirrhosis and splenomegaly. Numerous pathologists were quick to point out that the "fibroadenic" was a non-specific lesion which represented a response of the splenic reticulum to increased portal tension and chronic splenic congestion.[21-26] The terms "Banti's Syndrome" or "Splenic Anemia" persisted, however, and were applied to those instances of portal hypertension in which splenomegaly with secondary hypersplenism were prominent features of the clinical course, representing a vastly different concept from that which Banti had described. Rousselot,[17] Larrabee,[27] and Thompson[25] emphasized that all the changes in the spleens of "Banti's Syndrome" were the result of an obstruction in

the portal circulation with a resultant "congestive splenomegaly".

The bulk of evidence accumulated since the publication of Banti's papers towards the turn of the century seemed to adequately refute the idea that the disease Banti described was a clinical or pathologic entity. In 1940, however, Ravenna[28] emphasized that the theory of congestive splenomegaly secondary to portal venous obstruction failed to explain those cases of portal hypertension in which no obstructive factor could be demonstrated. He reiterated the concept that in such cases a splenic lesion might be involved, but rather than the elaboration of a splenic toxin, he postulated an increased flow of blood through the spleen as of primary etiologic significance. Without producing any experimental or pathologic observations Ravenna suggested that the small splenic arterioles were the site of early lesions which allowed blood to enter the spleen in increased amounts, leading to splenic congestion and increased intrasplenic pressure, Splenic fibrosis and hyperplasia were felt to be directly related to the persistent splenic engorgement, while the hypertension led to dilatation of the splenic and portal veins with their eventual thrombosis. He further related the final development of hepatic cirrhosis (Banti's third phase) to the increased blood flow and primary portal hypertension. In a subsequent paper[29] Ravenna presented clinical evidence to demonstrate that chronic passive hyperemia of the spleen does not in itself invariably lead to significant splenomegaly. He pointed out that the Banti spleen weighs more than 1000 grams, and that congestion alone does not produce splenic enlargement approaching that size. With the chronic passive congestion of the spleen in chronic cardiac failure, in fact, there is frequently a reduction in size of the spleen

(cyanotic atrophy). Experimentally, splenic congestion by partial portal vein obstruction in rabbits was not followed by splenic enlargement within six months.[30] Partial constriction of the splenic vein of the dog with ligation of the splenic collateral vessels produced little increase in splenic size after six months to two years.[26]

There is little direct evidence to substantiate Ravenna's theory. Complete denervation of the spleen of the dog leads to an initial increase in volume of the organ but with subsequent shrinkage.[31] Henschen and Howald[32] observed a two-fold increase in the splenic weights of two dogs within six and one-half months following denervation of the spleen. Histologically, the sinuses were congested, but no proliferative or fibrotic changes were described. Pathological confirmation of the arterial lesions Ravenna suggested has not been obtained. Perhaps of greater significance than the hypothesis which Ravenna proposed, however, was the fact that he recognized that portal hypertension could occur in the absence of obstruction and that in such cases increases in portal flow might be important.

Since Ravenna's papers published reports emphasizing portal hypertension without portal obstruction have been few. Pemberton and Kiernan[33] in 1945 also observed that the hypothesis of mechanical obstruction in the development of splenomegaly failed to explain portal hypertension in the absence of cirrhosis or extrahepatic portal block. These authors felt that in such cases the splenic enlargement was primary and due to an increased blood flow to the spleen as a response to infection, pulp hyperplasia or a primary derangement of the mechanism controlling the activity of the splenic vasculature. Foster[34] in 1954 referred to Ravenna's papers and suggested that the term

"Banti's Syndrome" be reserved for those cases with intra- or extrahepatic obstruction and with splenomegaly, varices, anemia and leukopenia. Hallenbeck and Schocket[35] reported 55 patients treated by porta-caval shunts. Three of these had no roentgen evidence of hepatic or extrahepatic obstruction, and liver function tests were normal. Liver biopsies revealed only "increased fibrous tissue and venous spaces in the periportal tissues". No explanations of pathogenesis were attempted in these instances. In the most complete study to date Tisdale, Klatskin and Glenn[36] are reporting four cases of non-obstructive portal hypertension manifested by massive hematemesis from esophageal varices with normal liver function and structure. Splenoportograms demonstrated no obstructions in the portal vascular bed, and all had elevated portal venous pressures determined at laparotomy. There was splenomegaly in two cases, and liver biopsies in two patients revealed only minimal periportal fibrosis. Biopsies were normal in the remaining two patients. Repeat biopsies two and four years after porta-caval shunts demonstrated no progression of the hepatic lesions. The authors discuss the factor of increased blood flow as an etiologic factor to account for the increased portal tensions and suggest the possible existence of arterio-venous anastomoses. to account for increased flows. It is also suggested that a functional increase in the intrahepatic or portal venous tone could lead to increased vascular resistance and pressure.

Clinical examples of increased portal flows secondary to arterio-venous fistulas are uncommon. Occasionally, not invariably, these have been associated with the development of portal hypertension, esophageal varices, and occasionally ascites in the absence of intra-

hepatic disease. Although the cause of the fistulas may be traumatic, they appear to be more commonly a developmental malformation. Two cases of hepatic artery-portal vein fistulas have been reported.[37,38] Both became manifest by massive hematemesis, and both had normal livers at autopsy. Cassel et al[39] have reviewed the cases of arteriovenous fistulas of the splenic vessels with portal hypertension, hematemesis or ascites. In the case which they reported the lesion was demonstrated by aortography and was presumed to be the result of a bullet wound to the left lower thorax eleven years previously. Their patient had ascites with an enlarged but histologically normal liver. The BSP retention was 34% before operation, falling to 6% after splenectomy. In the six previously reported cases reviewed in this report two were associated with ascites and four had gastrointestinal bleeding. In two cases portal venous pressures of 35 and 43 cm. of water were recorded. In the well-studied case of Sigwart[40] an arterio-venous aneurysm was located three centimeters from the hilus of the spleen, and the portal vein pressure measured 43 cm. The patient had had repeated episodes of hematemesis for nine years. After ligation of the aneurysm the omental vein pressure fell to 15 cm., and after splenectomy the esophageal varices disappeared. Of particular interest is the observation that there were no changes in the liver after nine years of portal hypertension.

Owen and Coffey[41] reviewed 198 cases of splenic artery aneurysm and found positive evidence of portal hypertension in 20 percent without any other cause for the increased portal pressures. No apparent fistulous connection with the splenic vein existed in these cases. The authors compare a 1 percent incidence of splenic artery

aneurysm in cases of portal hypertension with a 0.037 percent incidence in the general population.

Recently, direct evidence for the existence of arterio-venous shunting in cases of "Banti's Disease" has been suggested by Womack and Peters.[42] In several of their cases at operation palpable thrills were detected in branches of the portal vein or in the hemiazygous vein. Oxygen saturations as high as 92 percent were found in the hemiazygous vein, suggesting arterio-venous shunting into the azygous and peri-esophageal venous system. In the same report an experimental study in dogs attempting to demonstrate the activity of arterio-venous shunts within the portal system was presented. They observed that the oxygen saturation of the portal venous blood fell to 69 percent of control following partial occlusion and to 73 percent of control after complete occlusion of the portal vein for five to fifteen minutes. At the same time the oxygen saturation in the inferior vena cava fell to 49 percent and 37 percent respectively of the control values. Upon release of the occlusion the oxygen saturation returned to normal or near normal levels. Occlusion of the hepatic artery alone caused no change in oxygen saturation within either vessels. If both the portal vein and the hepatic artery were occluded for two to fifteen minutes, thereby rendering the liver anoxic, and then the portal vein was again occluded five to ten minutes the oxygen saturation in the portal vein fell to 46 percent of control, whereas the inferior vena cava oxygen saturation remained at control levels. The authors concluded from these experiments that the preservation of the oxygen saturation of the portal venous blood after occlusion of the portal vein was due to the activity of arterio-venous shunts. They suggest further that these

shunts are under the control of a humoral agent which is sensitive to hepatic anoxia. Anatomic evidence for the existence of such shunts in the gastro-intestinal tract has been presented by Barclay and Bentley[43] who observed a shunting mechanism in the stomach submucosa of cadaver and operative specimens by a microarteriographic technique. Whether these shunts are present and active throughout the intestinal tract remains to be demonstrated.

Perhaps of significance in view of Womack's suggestions that there may be direct shunting of arterial blood into the azygous and esophageal venous systems are the accumulating reports of symptomatic esophageal varices occurring in the absence of portal hypertension.[44-46] Palmer and Brick[47] found thirteen such cases among 350 patients with esophageal varices demonstrated by esophagoscopy. Nine of the thirteen had had upper gastro-intestinal bleeding, and all had normal livers microscopically and functionally. Even in the presence of cirrhosis with hemorrhage from bleeding varices Dye[48] reported four patients who had normal portal pressures, suggesting either that portal hypertension is not necessary for the existence of bleeding varices or that there may be considerable fluctuation of portal pressures. The supposition that esophageal varices and hemorrhage are the sole result of elevated portal pressures has been questioned by Taylor[49] who observed an aggregate pressure of 160 cm. water, three times the highest portal pressures observed at laparotomy, in the distal esophagus during a reversed Valsalva maneuver. Baronofsky[50] has suggested that the acid-peptic factor may be of greater importance in the actual bleeding of varices. In a skeptical critique of surgically created venous shunts in the therapy of bleeding varices Nachlas[51] has summarized the data against

the supposition that portal hypertension is solely responsible for variceal hemorrhage. He points out that esophageal varices have been found in the absence of portal hypertension, that not all patients with varices bleed from them, that the occurrence of bleeding does not correlate with the degree of portal pressure, that varices may persist and bleed again following lowering of the portal pressure by operation, and that varices which have disappeared following venous shunting may return even though the portal pressure remains low. Evidence therefore exists that portal hypertension per se is not the sole factor in the pathogenesis of esophago-gastric varices nor for the hemorrhage which may result from them. It is conceivable that the discrepancies observed may be the result of variations in volume flow through the submucosal esophageal veins or localized venous stasis[52] without significantly elevated venous pressures.

Understanding of the pathogenesis of portal hypertension has been handicapped by the inability to reproduce the syndrome in the experimental animal as it exists in man. Most studies have utilized the dog as the experimental animal, although the rat, cat and monkey have also been studied.

A number of approaches have been utilized by different investigators, and these have been reviewed by Wiles[53] and Taylor[54]. Essentially, three different methods have been tried: The effect of experimentally induced hepatic cirrhosis, the effect of obstructing the vascular outflow or inflow of the liver, and the effect of the introduction of blood at arterial pressures directly into the portal system by a variety of surgically produced arterio-venous fistulas.

Opinion differs upon what constitutes normal portal venous pressures in the dog. In the carefully controlled experiments of

Hoffbauer, Bollman and Grindlay[55] the average portal venous pressure of the unanesthetized dog was 6.4 cm. of water with a range of three to seven centimeters. Using pentobarbital anesthesia Douglass, et al[56] report normal portal pressures of 10-15 cm. of water, whereas Taylor[53] accepts any pressure below 30 cm. as normal for the dog.

Hepatic cirrhosis can be produced in the dog by the repeated injection of fine suspensions of silica. Taylor[53] followed five dogs with silica cirrhosis for one to three years, and their portal pressures remained between 20 and 30 cm. of water. Volwiler, Grindlay and Bollman[57] produced a silica fibrosis in ten dogs over a period of sixteen to twenty-five months and observed portal pressures of 15.5 to 28.0 cm. of water. These animals developed large collateral vessels involving the retroperitoneal, paraesophageal, abdominal wall, azygous, diaphragmatic and hemorrhoidal veins. Two animals developed enlarged submucosal esophageal veins but no true varices. The production of cirrhosis by the administration of carbon tetrachloride produced portal pressures of eight to fifteen centimeters of water.[55]

Detailed studies have been made of the pressure changes in the portal vein and inferior vena cava of the unanesthetized dog following the partial or complete occlusion of the vascular inflow and outflow of the liver, the inferior vena cava and the azygous vein both singly and in various combinations.[58,59] Acute occlusion of the inferior vena cava or the portal vein is fatal to the dog, unlike man or the monkey who tolerate these procedures without difficulty. With acute occlusion of the portal vein of the dog there is an immediate fall in arterial pressure with a rise in portal pressure to 30-35 cm. of water. Complete occlusion of either the portal vein or inferior

vena cava may be achieved, however, if the procedure is staged. In none of these experiments has the portal venous pressure exceeded 27 centimeters of water and in none have esophageal varices been produced. The inability to produce significantly elevated portal pressures by these methods seems to be related to the rapid development of an extensive collateral circulation around the site of the block. Perfusion studies of the portal circulation of the dog following portal vein constriction have demonstrated the main collaterals to be the periesophageal, hepatoduodenal, retroduodenal, splenorenal, omental and retrocolic veins.[60] The coronary-esophageal shunt may account for as much as 50 percent of the total shunt flow, and the periesophageal veins become markedly dilated, although the intramural esophageal veins remain normal.

Obstruction of the venous outflow of the liver does not result in portal hypertension, but it does represent the most effective means to produce experimental ascites. Numerous observers have stressed the inconstancy of the presence of ascites in relation to the presence or degree of portal hypertension.[61-64] Experimentally, however, ascites can be consistently produced by any procedure which will effectively obstruct the hepatic venous outflow with resultant hepatic engorgement and elevated hepatic venous pressures. Practically, this has been achieved in dogs by constriction of the thoracic inferior vena cava,[65,66] hepatic vein ligation,[67] right heart pericardial constriction,[68] experimental tricuspid insufficiency,[69] and by anastomosis of the thoracic inferior vena cava to the right pulmonary artery.[70] The effect is a transient one, since the ascites will disappear with eventual collateral by-pass of the obstruction and relief of the hepatic venous engorgement. Holman and Parsons[68] demonstrated that the ascites would reoccur with

subsequent constriction of the superior vena cava. The source of the ascitic fluid is felt to be a transudate from the hepatic capsular lymphatics.[63,71,72] The hepatic pathology produced by chronic thoracic inferior vena cava constriction has been studied by Zimmerman and Hillman[73] who observed pericentral congestion, necrosis and fibrosis with subcapsular sinusoidal dilatation. Eventually, pseudolobule formation with bands of connective tissue between hepatic veins was observed.

Hypoproteinemia and salt and water retention are also important factors in the pathogenesis of ascites.[74] McKee, Schilling, et al[65] studied the ameliorating effect of a high protein diet upon the ascites following constriction of the thoracic inferior vena cava. With the rise in serum protein, however, there was a concurrent rise in ascitic protein, demonstrating the free exchange of protein between the plasma and ascitic fluid. Studies of the effect of sodium chloride ingestion upon experimental ascites reveal a reduction in ascites formation with a low sodium diet and a prompt increase in fluid retention with increase in the sodium consumption.[75,76] Salt and water retention have been related to an increased aldosterone secretion in these experimental preparations.[77] It is emphasized, however, that this adrenal response is secondary to the extravasation of fluids and electrolytes and that the elevated hepatic venous pressure is the primary event leading to the accumulation of fluid in the peritoneal cavity.

The post-mortem perfusion of cirrhotic livers from patients with or without ascites has emphasized the degree of hepatic venous obstruction in the development of ascites.[9] In cirrhosis with irreversi-

ble ascites there is an absolute and compensatory increase in the portal venous and hepatic arterial vasculature with an absolute decrease in the hepatic venous bed. Where there was clinically absent or reversible ascites the liver showed a symmetrical deficit in all the intrahepatic vascular systems, especially the hepatic and portal venous beds. It was felt that the cause of irreversible ascites with cirrhosis was due to an obliterative fibrosis of the hepatic veins, whereas with reversible ascites the hepatic venous obstruction was believed to be due to diffuse intrahepatic cellular edema secondary to both protein and electrolyte imbalance. This concept of the importance of hepatic venous obstruction of the pathogenesis of ascites has been utilized by McDermott[62] in the surgical treatment of ascites by combining both portal and hepatic venous decompression by means of a "double shunt".

This explanation, however, does not explain the uncommon cases of extrahepatic portal obstruction which <u>are</u> associated with ascites. Baggenstoss and Wallaeger[78] reported fifteen cases of chronic portal vein thrombosis without associated liver disease. In five of these ascites was present. It seems that in these cases, therefore, portal hypertension per se must be an important factor in the genesis of ascites. In experimental animals constriction or ligation of the portal vein alone does not produce ascites. If this procedure is combined with ligation of the abdominal vena cava and the induction of hypoproteinemia by plasmaphoresis a transient low-protein ascitic transudate is produced.[59] It is possible that the pathogenesis of ascites differs in these instances and that they are not comparable.

Attempts to produce portal hypertension in the dog by the production of various arterio-venous fistulae within theportal system have usually been incidental to study of the functional alterations following the arterialization of the liver. Significant and sustained elevations of the portal venous pressure have been obtained by these methods, however, and opportunity has been afforded to observe the effect of increased pressure and flow per se upon the hepatic vasculature and functions.

One of the earliest of these studies was that of Schilling[79,80] who implanted the hepatic artery into the portal vein of the dog. Eighteen months later portal pressures and liver biopsies were normal. In animals followed up to five years no portal hypertension or splenomegaly were observed. The livers, however, showed progressive fatty infiltration, sinusoidal dilatation and periportal fibrosis. Aneurysmal dilatations were present at the site of the anastomoses.

Cohn and Parsons[81,82] were the first to describe the technique of total arterialization of the liver. Their technique consisted of an end-to-side portacaval anastomosis with insertion of a venous autograft between the aorta and the proximal portal vein. Portal pressures two weeks after this procedure were three to four times the control values, averaging 31 cm. Vascular changes resembling an acute necrotizing vasculitis were described in the portal venous radicles.[83] Numerous vessels showed internal fibrosis and medial hypertrophy. Severe jaundice was also noticed in a few animals postoperatively.

The vascular lesions observed by Cohn resembled those described by Ferguson and Varco[84] in the pulmonary circulation. These

authors anastomosed the subclavian or brachiocephalic artery of the dog to the pulmonary artery and observed irreversible medial hypertrophy and intimal proliferation, often progressing to obliteration, in the pulmonary arterioles two or more weeks following operation. They felt that increased vascular pressure was of greater significance than increased flow in producing the vascular lesions. Changes in the larger portal vessels have also been studied in patients with portal hypertension.[85,86] These have shown intimal thickening and medial hypertrophy, presumably caused by the increased venous pressures. In the few well-studied cases reported similar changes in the intrahepatic portal venules have not been observed in patients with increased portal tensions but without liver disease or vascular obstruction.[36]

On the other hand, Fisher et al[87] studied 85 dogs prepared in a manner similar to those of Cohn and observed up to 106 days postoperatively. In the long-term survivors the livers were grossly and microscopically normal; no vasculitis or hypertrophied venous radicles were observed. Additional observations on these animals demonstrated a two-fold increase in hepatic blood flow, a one and one-half fold increase in cardiac output, a two-fold increase in hepatic glucose production and an unchanged splanchnic oxygen consumption. All of these parameters tended to return towards normal thirty days or more after operation, associated with progressive narrowing and eventual thrombosis in the main portal vein near the site of the anastomosis. In several animals cytoplasmic acidophilic inclusions were described within hepatic parenchumal cells.[88] Histochemically, these were unsaturated, non-lipid, protein complexes resembling similar inclusions observed following partial hepatectomy. Additional effects observed

in dogs with totally arterialized livers included an enhanced hepatic regenerative capacity[89] and a reduction in fatty acid content following an Eck fistula.[90]

Servello and Pelionio[91] arterialized the liver by performing a latero-latero anastomosis of the aorta to the splenic vein. No change in the liver was observed after "several months".

Whereas some have utilized arterio-venous shunts as a method to produce experimental portal hypertension, others[92] have suggested the same technique as a therapeutic method for the treatment of portal hypertension. Five patients with cirrhosis have been treated by this method, and four are known to have died.[52] Follow-up data on the fifth patient is unavailable;[93] there was little change, however, in the wedged hepatic venous pressure one month following end-to-side portacaval shunt with anastomosis of the right gastro-epiploic artery to the proximal portal vein.

In order to further elucidate the long-term effect of an increased blood flow per se upon the function and structure of the liver and of the portal venous system of the dog a new experimental method has been developed. It is proposed to increase the blood flow to the liver by the creation of a reversed Eck fistula together with an aortic-caval fistula. By ligating the inferior vena cava below the fistula arterial blood has been directed into the portal vein by way of the reversed portacaval shunt. Continued studies over a period of months will be directed at determining changes in flow and portal pressures along with observations of hepatic structure and function.

METHODS

Adult mongrel dogs were used in this study. Hepatic blood flows were determined before and after the creation of the vascular shunts by the bromsulfalein clearance method of Bradley.[94]

The animals were anesthetized with Nembutal, 30 mg/kg. The left and right external jugular and the left femoral vein were exposed. The left external jugular vein was cannulated with a polyethylene catheter connected by a 3-way stopcock to a heparin-saline infusion for the sampling of peripheral venous blood. Under fluoroscopic control the right or left hepatic vein was then catheterized with a No. 8 cardiac catheter via the right external jugular vein and connected to a 3-way stopcock and saline-heparin infusion. The hepatic catheter was wedged and then withdrawn about one centimeter so that a free flow of hepatic venous blood was obtained. The left femoral vein was then catheterized, and a priming dose of BSP, 4 mg/hg. was given intravenously. Immediately following the priming dose the catheter was connected to a mercury displacement constant infusion pump,[95] calibrated to deliver a 150 mg.% solution of BSP at a rate of about 1 cc/min., so as to deliver about 1.5 mg./cc/min., and the time was recorded. Thirty minutes were allowed for stabilization of the peripheral blood BSP levels. Then six simultaneous 5 cc. blood samples were withdrawn at ten minute intervals into heparinized and siliconized syringes from the hepatic and left external jugular veins and placed in labeled siliconized centrifuge tubes. Five cc. specimens were withdrawn and discarded immediately before the samples in order to eliminate the catheter dead space, and the samples were withdrawn over a one minute interval in order to reduce hemolysis to a minimum. Following the last samples the

BSP infusion was stopped, the time recorded, the catheter removed and the incision closed.

Following determination of the microhematocrits of the six peripheral blood samples all the samples were centrifuged for 20 min. at 20 RPM, and the plasma was separated from the cells. Badly hemolyzed specimens were discarded. The plasma samples were then analyzed for their BSP content using a Coleman Spectrophotometer at an absorption of 580 mu. Duplicate samples were prepared of 0.5 cc. plasma and 2.0 cc. normal saline. Following the adjustment of each sample to 100% transmission two drops of 1.0 N NaOH were added, the sample mixed to develop the color and the percent transmission determined. If the transmission were less than 30 percent additional dilution was required. The concentration of the infusate was determined similarly. From the percent transmission the concentration of BSP was determined from a standardized graph, prepared from the transmission properties of varied dilutions of known BSP concentrations (courtesy of Dr. Milton Hales, Department of Pathology).

The Estimated Hepatic Blood Flow (EHBF) was then calculated using the formula proposed by Bradley.[94]

$$\mathrm{EHBF} = \frac{R}{0.01(P-H)} \times \frac{1}{1-\mathrm{Hct}}$$

Where R = total BSP removal rate

rate of BSP infusion, mg/min.

P = concentration of BSP in peripheral blood, mg.%

H = concentration of BSP in hepatic venous blood, mg.%

Hct = microhematocrit

If the peripheral BSP concentration is not constant in successive samples, a correction must be made for the BSP removal rate (R):

$$R = I \pm (AP \times V)$$

Where R = total BSP removal rate, mgm/min.

I = rate of BSP infusion, mg/min.

AP = rate of change of peripheral BSP concentration, mg/ml/min.

V = plasma volume

= 10.2% of the body weight[96]

Samples in which P_{BSP} varied more than 0.0005 mg/ml/min. were discarded.

A reversed portacaval shunt was subsequently performed, exposing the portal vein and inferior vena cava by a right thoraco-abdominal incision through the bed of the ninth rib. A liver biopsy was taken, and pre-shunt pressures were recorded in the portal vein and inferior vena cava with a water manometer, corrected to the level of the portal vein. A side-to-side two centimeter anastomosis was performed between the portal vein and inferior vena cava, doubly ligating the vena cava above the anastomosis. The left adrenal vein and the three left lumbar veins were identified, ligated and divided. Post-shunt pressures were recorded, and the incisions closed.

After allowing a suitable time for recovery a second operation was performed in which the aorta and inferior vena cava were exposed through a lower midline abdominal incision. A one centimeter arteriovenous fistula was constructed just above the inferior mesenteric artery, and the vena cava was ligated below the anastomosis. Pressures were recorded in the vena cava and mesenteric vein before and after construction of the fistula. Postoperatively the dogs were digitalized. After recovery liver blood flows were again determined as previously described.

RESULTS

Data are presented for one animal in which a reversed Eck fistula and an aortic-caval fistula have been constructed. Following the second operation a loud bruit has remained audible over the animal's lumbar spine. Liver blood flows, portal venous and inferior vena cava pressures were recorded before and after construction of the vascular shunts. These data are summarized in Table I and II.

It will be observed that the mean estimated hepatic blood flow, as determined by the BSP extraction method, increased from 40.1 cc/kg/min. to 97.0 cc/kg/min., an increase of 2.4 times. There was an 8.5 cm. rise in portal venous pressure following the reversed Eck fistula, and the inferior vena cava pressure was 19.6 cm. following completion of both shunts.

A liver biopsy taken at the time of the first operation demonstrated a normal liver structure.

TABLE I

COMPARISON OF ESTIMATED HEPATIC BLOOD FLOW (EHBF)

Dog #5 - Wt. 26.5 kg.

A. Pre-Shunt

Sample #	PBSP mg.%	HBSP mg.%	P-H mg.%	R mg/min.	Hct.	AP mg/ml/min.	EHBF cc/kg/min.
1	1.195	0.795	0.400	1.42	50	0	26.8
2	1.285	1.035	0.250	1.30	49	0.00009	38.6
3	1.690	1.435	0.255	1.17	53	0.0002	36.9
4	1.760	1.505	0.255	1.33	52	0.00007	41.1
5	1.880	1.720	0.160	1.26	52	0.0001	57.2

Mean = 40.1 ± 11.0

B. Post-Shunt

(14 Days PO)

Sample #	PBSP mg.%	HBSP mg.%	P-H mg.%	R mg/min.	Hct.	AP mg/ml/min.	EHBF cc/kg/min.
1	0.495	0.420	0.075	1.50	24	0	100
2	0.450	0.340	0.110	1.59	24	0.00005	72.1
3	0.465	0.415	0.050	1.47	23	0.00002	145
4	0.470	0.365	0.105	1.49	24	0.00001	70.8

Mean = 97.0 ± 34.7

TABLE II

COMPARISON OF EHBF, PORTAL VEIN AND INFERIOR VENA CAVA PRESSURES

	PPV Cm.H_2O	PIVC Cm.H_2O	EHBF cc/kg/min.
Pre-Shunt:	10.8	8.5	40.1
Post-Portacaval Shunt:	18.3	17.3	----
Post-Aortic-Caval Shunt:	24.8*	28.1	97.0

* Uncorrected pressure in mesenteric vein

DISCUSSION

The experimental approaches to the study of the pathogenesis of portal hypertension have been extensively reviewed in the first part of this paper. It was emphasized therein that a considerable body of evidence exists which implicates increased portal venous blood flow as a responsible factor in rare cases of portal hypertension. The method which has been described represents an attempt to investigate the effects of persistently elevated hepatic flows in the dog over a period of perhaps several years. It is proposed to study these animals with intermittent liver biopsies, liver function tests, hepatic blood flows, wedged hepatic venous pressures and esophagoscopy. Although the details of the method are unique it is fully recognized that others, notably Schilling,[80] Cohn[82] and Fisher,[87] have utilized similar techniques to obtain comparably increased hepatic blood flows in the course of investigating certain other aspects of hepatic physiology. Any uniqueness which this method may possess may lie solely in that it is being directed at a study of the relations, if any, of increased hepatic flows to experimental portal hypertension in the dog over a lengthy period of follow-up study. It may well be that the failure of all attempts to produce portal hypertension experimentally may simply represent a species variation. The facility whereby the dog develops a collateral circulation following portal bed obstruction is conspicuous in the absence of the utilization of the esophageal submucosal vessels, representing perhaps an anatomical or functional variation from the human organism. Child[1] has already shown that the macaque responds to acute portal vein occlusion in a manner similar to man, and it would be of interest to

evaluate the effects of increased portal flows in this species.

The hepatic blood flows measured in this experiment utilized the Bromsulfalein extraction method which was first introduced by Bradley.[94] The method is an application of the Fick principle, and its validity has been generally accepted. Bradley extensively discussed the assumptions which must be made in order to utilize this method. Paramount among these is that the liver is the only significant site for BSP removal, so that the BSP concentration in a peripheral vein or artery is the same as that in the portal vein. In the experiment described in this paper it must be further assumed that following the production of the vascular shunts no BSP reaches the liver before it reaches the right atrium, since the concentration of BSP is higher in the inferior vena cava than in the external jugular vein where the blood is sampled. The high venous pressure proximal to the ligated vena cava makes this assumption a reasonable one.

Sapirstein and Reininger[97] have emphasized the catheter induced error in hepatic venous sampling, demonstrating increasing vena cava reflux as the catheter is withdrawn from its wedged position. They pointed out also that local resistance changes produced by deeply placed catheters are of importance in determining the portal inflow to the catheterized area. Pratt, et al[98] demonstrated that changes in the rate of dye infusion produced proportional changes in the BSP extraction rate up to a maximum limit. An important limitation of the method was emphasized by Russ, et al[99] and became evident in this study. With increasing hepatic blood flows the extraction rate of BSP falls, so that the concentration of BSP leaving the liver approaches that entering the liver. With the high flows produced by the vascular shunts P_{BSP} and

H_{BSP} occasionally fell within the error of the analysis itself, necessitating elimination of the sample.

Determination of the estimated hepatic blood flows in four normal dogs in this laboratory has given an average value of 42.0 cc/kg/min. (40.1-45.6), in essential agreement with other observers using the BSP and other methods.[100] The wide variations that may be observed in the hepatic blood flow in a given animal at different times have been noted by Casselman and Rappaport.[101] They observed variations from one sampling period to another in the same animal ranging from 45 percent less to 57 percent more than the preceding values. In a given series of measurements the flows varied from 8.5 to 76 percent greater than the minimum value. Werner and Horvath[102] observed similar wide spontaneous variations and emphasized that a single observation represents only the blood flow under the conditions during that period of observation. Such wide variations were not as notable in the present series. Other investigators[103,104] using methods other than the BSP method have observed similar wide variations in the hepatic blood flow. These observations lend greater significance to the direct hepatic illumination studies of Wakim and Mann[9] and their conclusion that much of the hepatic circulation may be inactive at any given moment.

SUMMARY

(1) The clinical, pathologic and experimental factors in the pathogenesis of portal hypertension are reviewed.

(2) Particular attention is drawn to the occasional existence of portal hypertension in the absence of any demonstrable portal vascular obstruction. The possible significance of increased portal venous blood flow as an etiologic factor in the elevated portal pressures of such cases is discussed.

(3) A method is described for the production of increased portal blood flow in the dog in an attempt to study the long-term effects of elevated flows upon the hepatic structure and function and portal vasculature. In one animal reported the hepatic blood flow, determined by the Bromsulfalein extraction method, was increased 2.4 times following construction of a reversed Eck fistula and an aortic-caval fistula.

(4) Experience with the determination of the estimated hepatic blood flow by the Bromsulfalein extraction method is reported, and the limitations of the technique are discussed.

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